REMARKS

Claims 1-17 and 21-26 are currently pending. Claim 1 is presently amended to further clarify that the oligomers or co-oligomers which substitute the hydrophilic polymers are at least partly formed by chiral monomers, such that the oligomers or co-oligomers in mixture (A) have complementary chirality to those in mixture (B). Support for the claim amendments can be found, for example, at page 10, line 21 through page 11, line 1, which describes oligomers or co-oligomers for preferred embodiments. No new matter has been introduced by way of these amendments. Applicants respectfully request entry of the amendments to the claims and reconsideration in view of the following remarks.

Rejections under 35 U.S.C. § 102(b)

The Office has maintained its rejection of claims 1-5, 7-10 and 13 under 35 U.S.C. § 102(b), as allegedly being anticipated by Okihara *et al.* (J. Macromol Sci. Phys. (1991) B30 (1&2) 119-140). The Office has also maintained its rejection of claims 1-10, 14 and 21-26 under 35 U.S.C. § 102(b), as allegedly being anticipated by Hennink *et al.* (WO 98/00170). Applicants respectfully disagree and request reconsideration in view of the following.

With regards to the alleged anticipation by Okihara *et al.*, the Office alleges that the stereocomplex mixture disclosed by Okihara *et al.* inherently forms a hydrogel. The Office also alleges that, as the properties of a composition cannot be separated from the composition itself, the stereocomplex of Okihara *et al.* would inherently have the properties of claims 3-5, 8-10 and 13, even though Okihara *et al.* fails to teach an aqueous system. Further, the Office alleges that Applicant's Example 6 confirms a hydrogel for Okihara.

To anticipate a claim, the reference must teach each and every element of the claim. Applicants respectfully submit that Okihara *et al.* fails to anticipate claims 1-5, 7-10 and 13 of the present invention because if fails to teach each and every element of the claims.

Okihara *et al.* teaches a stereocomplex formed by crystallization of an equimolar mixture of poly(L-lactide) and poly(D-lactide) from 0.04% acetonitrile in p-xylene The poly(L-lactide) and poly(D-lactide) polymers described by Okihara *et al.* are reported to have molecular weights ranging from 5,000 to 300,000. *See* Okihara *et al.*, page 120, second paragraph. Based on the reported molecular weights, a person of skill in the art would estimate the polymer lengths range from about 69 monomer units to more than 4,100 monomer units (estimating each monomer contributes 72 to the polymer molecular weight). X-ray structure analysis of the crystalline stereocomplex revealed that the poly(L-lactide) and poly(D-lactide) polymer strands packed in a parallel fashion, generating a more stable and tightly packed complex than the poly(L-lactide) homopolymer. Okihara *et al.* also disclosed that not all optically active polyesters formed stereocomplexes. *See, e.g.*, Okihara *et al.*, Table 1, pages 122-123.

The stereocomplex of Okihara *et al.* fails to anticipate the claims of the present invention for the following reasons. First, poly(lactide) polymers do not constitute water soluble or water dispersible hydrophilic polymers. Poly(lactic acid) (PLA) forms a hydrophobic polymer (*see, e.g.* Huh *et al.* Drug Delivery Tech. 2003; 3:42, left column, second paragraph, noting that the biodegradable polyesters, including PLA, are all strongly hydrophobic) that is insoluble in water. *See* Hennink Decl. of Jan. 20, 2005, at paragraph 6.

Second, Okihara teaches a crystalline stereocomplex formed by crystallization from 0.04% acetonitrile in p-xylene with slow cooling from 54 °C. The system described by Okihara *et al.* does not contain water. Thus, Okihara *et al.* fails to teach a hydrophilic polymer in aqueous solution.

Third, the stereocomplex of Okihara is not substituted with oligomers or co-oligomers, wherein said oligomers or co-oligomers are at least partly formed from chiral monomers. Okihara *et al.* teaches a stereocomplex formed between an equimolar mixture of a poly(L-lactide) polymer and a poly(D-lactide) polymer. Each poly(lactide) homopolymer is a linear polyester generated by forming an ester linkage between the carboxylic acid moiety of one monomer and the alpha-hydroxy moiety of the adjacent monomer. These poly(lactic acid) homopolymers are incapable of

substitution because they do not contain any functionality available for further chemistry. *See, e.g.* Elisseeff *et al.*, Macromolecules 1997; 30:2182-2184, at 2182, left column, second paragraph (noting that PLA "has no functionality available for ...other further chemistry."). Accordingly, Okihara *et al.* fails to teach hydrophilic polymers substituted with oligomers or co-oligomers.

Because Okihara fails to teach a polymer substituted with oligomers or co-oligomers, it cannot satisfy the claim requirement that the chiral monomers which make up at least part of the oligomers or co-oligomers in mixture (A) have complementary chirality to those in mixture (B). For the same reason, Okihara cannot satisfy the claim requirement that the chiral parts of the oligomers or co-oligomers in the two polymer mixtures interact non-covalently.

As described in detail above, Okihara *et al.* fails to satisfy the limitations of claim 1, and thus does not anticipate claim 1. Because claims 2-5, 7-10 and 13 contain all the limitations of claim 1, Okihara *et al.* likewise does not anticipate these claims.

The Office's allegation that Applicant's Example 6 confirms a hydrogel for Okihara *et al.* mischaracterizes the example. Example 6 describes the synthesis of dextran polymers grafted with chiral poly(lactide) oligomers having an average oligomer length of 9 (i.e. $DP_{av} = 9$). In system I, the oligomer is attached to the dextran polymer via its terminal hydroxyl group (dex-lactate-MEE). In system II, the oligomer is attached to the dextran polymer via its terminal carboxylic acid (dex-lactate-acetate). The experiment studied whether stereocomplex formation between grafted oligomers would be enhanced if the oligomer having one chirality was selected from system I, while the oligomer having the opposite chirality was selected from system II. The results of gelation experiments for these grafted dextran polymers are presented in Table 5 on page 41. The reference to Okihara *et al.* in the example merely describes that parallel packing was observed for the Okihara stereocomplex. *See* Example 6, page 38, lines 17-20. All gelation experiments described in Example 6 refer to hydrophilic dextran polymers substituted with chiral poly(lactide) oligomers. *See* Example 6, page 40, line 15 through page 41, line 8. No gelation experiments were conducted using the stereocomplex described by Okihara *et al.*

Regarding the issue of inherency, Okihara *et al.* does not disclose the formation of hydrogels and there is no evidence of record to support the Office's assertion that the stereocomplex described by Okihara *et al.* inherently forms a hydrogel. The Federal Circuit has stated that: "[t]o serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

The Office is invited to identify any portion of the cited art or some other available reference that supports the assertion that the allegedly inherent property of the Okihara stereocomplex is necessarily present and would be recognized by a person of ordinary skill in the art. Alternatively, Applicants invite the Office to take official notice of the allegedly inherent principle taught in Okihara *et al.* so that the record can be made complete for appeal.

Because Okihara *et al.* fails to teach each and every element of the claimed invention, and there is no evidence of record to support the Office's assertion that the stereocomplex described by Okihara *et al.* inherently forms a hydrogel, Applicants respectfully request that the rejection of claims 1-5, 7-10 and 13 as anticipated by Okihara *et al.* be withdrawn.

With regards to the alleged anticipation of claims 1-10, 14 and 21-26 by Hennink *et al.* (WO 98/00170), the Office alleges that Hennink teaches a biodegradable hydrogel that meets the limitations of the claims. Applicants respectfully disagree.

Hennink *et al.* describes covalently crosslinked, biodegradable hydrogels as controlled release agents. The hydrogels taught by Hennink are prepared by free radical polymerization of crosslinkable groups, such as methacrylate groups. As the Office notes, poly(glycolic acid) or poly(lactic acid) spacers are introduced between the methacrylate groups and the dextran polymer. However, the hydrogels taught by Hennink *et al.* fail to meet the limitations of the claims for the following reasons.

First, as previously noted by the Applicants, Hennink *et al.* does not teach two polymer strands substituted with chiral oligomers or co-oligomers having opposite and complementary chirality, as required by claim 1. The hydrogel taught by Hennink *et al.* comprises only one polymer that is covalently crosslinked through free radical polymerization of a crosslinkable group such as methacrylate. The poly(glycolic acid) or poly(lactic acid) units described by Hennink *et al.* are incorporated merely as hydrolysable spacers between the methacrylate groups and the dextran polymer. There is no requirement that these spacers have complementary chirality, or are even chiral at all. As previously explained, the only reference to a chiral lactide in WO 98/00170 is in Example 3, which describes the synthesis of dextran-(L-lactide)-HEMA. In Example 5, dextran-(L-lactide)-HEMA polymer was polymerized with itself (*i.e.*, another methacrylated dextran coupled to an L-lactide) via crosslinking of the methacrylate groups, producing a single, covalently linked polymer wherein the chiral parts of the oligomers attached to the dextran contained the same chirality, not complementary (i.e. opposite) chirality as required by the claims. Other examples in Hennink *et al.* teach the use of achiral poly(glycolic acid) acid as a spacer, which is incapable of meeting the claim limitation requiring noncovalent interaction of two oligomers having complementary chirality.

Second, Hennink *et al.* does not teach two polymer strands containing complementary chiral oligomers that interact noncovalently, as specifically required by claim 1. Instead, Hennink explicitly teaches a covalently cross-linked polymer, wherein poly(glycolic acid) or poly(lactic acid) are incorporated as spacers between the dextran polymer and the methacrylate groups that undergo crosslinking by radical polymerization.

One of skill in the art would understand that the properties of the hydrogels taught by Hennink *et al.* are strikingly different than those of the claimed invention, as evidenced by their protein release characteristics. Hennink *et al.* describe the protein release characteristics for their biodegradable hydrogels as having zero order kinetics (i.e. cumulative release proportional to time). *See* Hennink *et al.*, Example 6, page 20, lines 6-7 and at Figure 5. By contrast, protein release from a hydrogel of the present invention displays non-zero order kinetics. *See, e.g.* Example 5, page 38, lines 4-12 and at Figure 12A.

The Examiner's comments regarding the method of synthesis, degree of substitution, methods of drug loading and microsphere preparation do not address the fundamental failure of Hennink *et al.* to meet the limitations of claim 1 by failing to disclose two polymers having complementary chiral oligomers that interact noncovalently with each other. Accordingly, Hennink *et al.* does not anticipate claim 1. Because claims 2-10, 14 and 21-26 contain all the limitations of claim 1, Hennink *et al.* also does not anticipate these claims. Applicants therefore respectfully request that the rejection of claims 1-10, 14 and 21-26 as anticipated by Hennink *et al.* be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 11, 12 and 15-17 remain rejected under 35 U.S.C. § 103(a). The Office alleges that claim 11 is unpatentable over Hennink *et al.* (WO 98/00170), claim 12 is unpatentable over Okihara *et al.*, and claims 15-17 are unpatentable over De Jong *et al.* (Macromolecules, 1998, 31:6397-6402) in view of Brannon-Peppas (Int. J. Pharm., 1995, 116:1-9). Applicants respectfully disagree and request reconsideration in view of the following.

To establish a *prima facie* case of obviousness, the Office must provide one or more references that, *inter alia*, teach all the limitations of the claimed invention and provide some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the references to achieve the claimed invention. The Office's obviousness rejection of the pending claims fails to meet either of these requirements. The references cited by the Office do not establish a *prima facie* case of obviousness because they neither teach all the limitations of the claimed invention nor provide motivation to one of ordinary skill in the art to combine the cited references to achieve the claimed invention.

The Office has maintained its rejection of claim 11 as unpatentable over Hennink *et al.*. To support this assertion, the Office specifically points to Hennink at page 9, lines 31-34, which states that an increasing degree of substitution (DS) yields a more crosslinked network. The Office

alleges that it would therefore have been obvious to a person of skill in the art to prepare a stereocomplex hydrogel as required by claim 11. Applicants respectfully disagree.

Applicants note that claim 11 contains all the limitations of claim 1. As discussed above, Hennink *et al.* neither teaches nor suggests polymers substituted with complementary chiral groups that interact noncovalently with each other. The Office has failed to articulate a *prima facie* case of obviousness because it has not cited one or more references that teach both of these features, in addition to the other features of the pending claim. The Office has provided no justification for the assertion that it would have been obvious to a person of skill in the art at the time of the invention to replace a covalently crosslinked polymer containing achiral linkers or linkers of a single chirality with two polymers that interact noncovalently through chiral oligomers having complementary chirality. Thus, the Office has failed to carry its burden and the present rejection should be withdrawn.

The Office has maintained its rejection of claim 12 as unpatentable over Okihara *et al.* The Office asserts that Okihara *et al.* teaches a stereocomplex hydrogel, but is silent of the length of the monomer chains, and asserts that Applicants have not demonstrated that the average oligomer length of 7-15 monomers provides unusual results. As discussed in detail above, Okihara *et al.* neither meets the limitations of claim 1, from which claim 12 depends, nor teaches a hydrogel composition. Claim 12 requires that the oligomeric or co-oligomeric groups have an average chain length of 7-15 monomers. Okihara does not teach a polymer substituted with oligomers or co-oligomers, and the Office has not provided a motivation for one of ordinary skill in the art at the time of the invention to modify the unsubstituted homopolymers of Okihara to achieve the claimed invention. Accordingly, Applicants respectfully request that the rejection of claim 12 over Okihara *et al.* be withdrawn.

The Office has maintained its rejection of claims 15-17 as unpatentable over De Jong *et al.* in view of Brannon-Peppas. As the Office notes, De Jong *et al.* discloses stereocomplex formation between homopolymers of poly(lactic acid), as well as certain other copolymers containing chiral lactide monomers. These stereocomplexes were formed from polydisperse lactic

acid oligomers prepared using 2-(2-methoxyethoxy)ethanol as initiator and stannous octoate as catalyst at 130 °C until the lactide was molten. *See* De Jong *et al.*, at page 6399 and 6401.

The Office alleges that it would have been obvious to one of ordinary skill at the time of the invention to include an active ingredient in the stereocomplexes described by De Jong *et al.* in view of Brannon-Peppas, which discloses drug delivery systems using biodegradable microparticles containing poly(lactic acid), poly(glycolic acid), or their copolymers.

Even assuming, *arguendo*, that a person of skill in the art would have been motivated in view of Brannon-Peppas to include active ingredients in the stereocomplexes described by De Jong *et al.* (which Applicants do not concede), Applicants respectfully disagree that these references taken together render claims 15-17 obvious. The Office has provided no motivation or suggestion to combine that would lead to the formation of the hydrogels of the present invention.

First, the stereocomplexes described by De Jong *et al.* are not themselves hydrogels. As previously indicated in Professor Hennink's declaration, hydrogels generally contain from about 20 weight % to more than 99 weight % water, and in the absence of water, the stereocomplexes described in De Jong cannot form hydrogels. *See* Hennink Decl. II of April 19, 2006, at paragraph 3.

The failure of De Jong *et al.* to teach the preparation of hydrogels is not remedied by the combination with Brannon-Peppas, which merely describes the use of biodegradable polymers in controlled drug delivery. Thus, even if De Jong *et al.* and Brannon-Peppas were combined, the combination does not provide a process for the preparation of hydrogels, as provided by claims 15-17 of the present invention.

Neither De Jong *et al.* nor Brannon-Peppas, alone or in combination, discloses: (1) formation of two water soluble or water dispersible hydrophilic polymers substituted with chiral oligomers or co-oligomers at least partly formed from monomers having opposite chirality (claim 15, step b); or (2) mixing two such mixtures in an aqueous system such that the groups on the polymers interact noncovalently (claim 15, step c). The Office has provided no motivation or

suggestion to combine that would lead one of skill in the art at the time of the invention to combine the polymers taught by De Jong *et al.* and Brannon-Peppas with hydrophilic polymers substituted with oligomers or co-oligomers having complementary chirality, as described for the present invention. Accordingly, claims 15-17 are nonobvious under De Jong *et al.*, in view of Brannon-Peppas, and Applicants respectfully request that this rejection be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 313632001000. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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